UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/589,589	06/08/2000	Katherine A. High	CHOP-0019 / CHOP-0088U	1864

110 7590 01/20/2010

DANN, DORFMAN, HERRELL & SKILLMAN
1601 MARKET STREET
SUITE 2400
PHILADELPHIA, PA 19103-2307

EXAMINER	
SINGH, ANOOP KUMAR	

ART UNIT	PAPER NUMBER
1632	

MAIL DATE	DELIVERY MODE
01/20/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/589,589	HIGH ET AL.	
	Examiner	Art Unit	
	ANOOP SINGH	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 December 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,24,28,43 and 44* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-2, 24, 28, 43 and 44* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Finality of the previous office action of June 2, 2009 has been withdrawn and the prosecution on the merit has been reopened in view of new rejections.

Applicant's amendments and response filed December 2, 2009 has been received and entered. Claims 3-23, 25-27, 29-42 have been canceled, while claim 43 ahs been amended. Claims 1-2, 24, 28, 43 and 44 are pending and under consideration in the instant application.

Specification

The disclosure is objected to because of the following informalities: The citation on page 13, line 9 is incomplete. Appropriate correction is required.

Maintained- Claim Rejections-in modified form - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-2, 24, 28, 43 and 44 were rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. Applicants' arguments filed December 2, 2009 have been fully considered and found persuasive in part, therefore, rejection of instant claims are modified. Claims 1-2, 24, 28, 43 and 44 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of preventing the formation of inhibitory antibodies to Factor IX delivered to a mammal by way of an adeno-associated viral vector, said method comprising
(i) intramuscularly administering an effective amount of an rAAV to a mammal, wherein said mammal has a genetic defect such that no detectable endogenous Factor IX protein is produced and wherein said mammal shows symptoms of hemophilia B, and (ii) intravenously or intraperitoneally administering to said mammal cyclophosphamide prior to or simultaneously with said adeno-associated viral vector delivery before formation of said inhibitory antibodies, thereby preventing the formation of inhibitory antibodies to Factor IX in said mammal, and

wherein said rAAV comprises a nucleic acid encoding Factor IX operably linked to an expression control element and the delivered Factor IX being from the same species as said mammal,

does not reasonably provide enablement for a method of preventing the formation of inhibitory antibodies to Factor IX delivered to a mammal having any other genetic defect which can result in generation of antibodies to Factor IX. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

This rejection is based on the absence of an enabling disclosure correlating to administering adneo -associated viral vector to a mammal that has any genetic defect other than genetic defect such that no detectable endogenous Factor IX protein is produced and wherein said mammal shows symptoms of hemophilia B resulting in generation of inhibitory antibodies to Factor IX. The deficiencies were identified by the Office after analysis of the disclosure provided in the instant application. In determining whether Applicant's claims are enabled, it must be found that one of skill in the art at the time of invention by applicant would not have had to perform "undue experimentation" to make and/or use the invention claimed. Such a determination is not a simple factual consideration, but is a conclusion reached by weighing at least eight factors as set forth in In re Wands, 858 F.2d at 737, 8 USPQ 1400, 2d at 1404. Such factors are: (1) The breadth of the claims; (2) The nature of the invention; (3) The state of the art; (4) The level of one of ordinary skill in the art; (5) The level of predictability in the art; (6) The amount of direction and guidance provided by Applicant; (7) The existence of working examples; and (8) The quantity of experimentation needed to make and/or use the invention.

The office has analyzed the specification in direct accordance to the factors outlines in *In re Wands*. MPEP 2164.04 states: "[W]hile the analysis and conclusion of a lack of enablement are based on factors discussed in MPEP 2164.01(a) and the evidence as whole, it is not necessary to discuss each factor in written enablement rejection." These factors will be analyzed, in turn, to demonstrate that one of ordinary skill in the art would have had to perform "undue experimentation" to make and/or use the invention and therefore, applicant's claims are not enabled.

The state of prior art effectively summarized by the reference of Herzog et al (Proc Natl Acad Sci U S A. 1997 May 27; 94(11):5804-9, IDS) and High et al (US Patent No. 6,093,392, IDS) teaches rAAV and adenovirus, has been used to effect expression of high levels of canine factor IX in immunodeficient/immuno-competent mice when the virus is administered in conjunction with immunosuppressive agent (column 1, lines 36-40 and Herzog abstract). High et al also discloses method of treating hemophilia in a mammal by administering an amount of rAAV comprising a nucleic acid encoding Factor IX operably linked to an expression control element to a mammal wherein said Factor IX is expressed at levels having a therapeutic effect on the mammal. The prior art is silent with respect to type of genetic defect in a mammal that could produce antibody to Factor IX. Given this lack of reasonable predictability in the art, the Artisan would require a large amount of information from Applicant's examples to provide the guidance to provide reasonable predictability.

The specification teaches a method for inhibiting the formation of inhibitory antibodies in a murine knockout model of hemophilia B undergoing rAAV gene therapy, said method comprising administering to said knockout mouse a recombinant AAV vector comprising murine factor IX (mFIX, $1x10^{11}$) in conjunction with anti-CD40L, cyclosporin A, or cyclophosphamide (pages 13-16). The results display that mice injected with AAV mFIX make Factor IX antibodies, which are inhibitory to the transgene product (page 15). Also, the results show that transgene expression may be increased with using an immunosuppressive agent in conjunction with delivering AAV comprising mFIX to the mice (pages 14-16). It is noted that specification describes the presence of inhibitory antibodies in a murine model of hemophilia which is caused by a large gene deletion affecting the promoter region and exons 1-3 of the F.IX gene resulting in complete absence of FIX transcript and protein. However, specification is silent with respect to type of genetic defect that could produce antibody to the Factor IX as required by the independent claim. The specification fails to provide an enabling disclosure for the claimed invention because the specification fails to provide sufficient guidance as to how an artisan of skill would have practiced the claimed method in any mammal that has any genetic defect that could produce Factor IX antibody. The guidance provided in the specification is limited to a mouse whose genome comprises a disruption in endogenous Factor IX gene such that no

functional protein is expressed, capable of producing Factor IX antibodies upon administration of rAAV comprising murine Factor IX.

Prior to instant invention, art teaches intramuscular administration of AAV comprising nucleic acid encoding canine F.IX to hemophilia dog. The results show intramuscular dose of AAV-cF.IX ($7x10^{13}$) to Dog 45 did not produce detectable antibodies specific for cFIX, as measured by Western blotting, ELISA assays and coagulation inhibitor screens at weeks 7, 13, 17, and 20. It is also reported that the dog B46 treated with higher dose had no detectable antibodies specific for cF.IX as measured by ELISA through week 9 (See High et al US Patent 6,093,392, col. 21, lines 8-65). It is further noted that High et al use a canine model of hemophilia, wherein dogs have a point mutation in the catalytic domain of the F.IX gene, that render the protein unstable thereby causing severe hemophilia B (See Evans et al., 1989, Proc. Natl. Acad. Sci. USA 86:10095-10099, IDS). In view of foregoing it is apparent that genetic defect caused by point mutation in cFIX gene in the mammal disclosed by High did not produce antibodies to Factor IX following intramuscular dose of AAV-cF.IX ($7x10^{13}$) to Dog. An artisan would have to perform undue experimentation to first identify the genetic defect that can produce antibody to Factor IX and then adminster rAAV comprising Factor IX to make and use the invention. Absent of evidence to the contrary, it is not clear that if any genetic defect in any mammal would be functional and capable of producing FIX antibodies in the same manner as they have been exemplified in prior art for a mouse whose genome comprises disruption in endogenous FIX gene such that no functional protein is made. Given, the lack of guidance provided by the specification it would have required undue experimentation for one of skill in the art to make and use the invention without a reasonable expectation of success.

The claims embrace administering rAAV serotype comprising nucleic acid encoding Factor IX to a mammal having any genetic defect that could produce antibody to Factor IX. In post filing art, Herzog et al suggested that both the underlying F.IX mutation is important in the inhibitor formation (see page 1289, col. 2, para. 3 in Herzog et al, Human Gene therapy, 13:1281–1291 2002). This is further supported by another post filing art that lists some of the factors that influence the risk of inhibitor formation in the setting of gene transfer include "[u]nderlying mutation, the vector itself, the route of administration, the presence or absence of a tissue-specific promoter, and the dose" (See Arruda et al Blood, 2004, 103(1) 85-92 page 91, col.

1, last para. to col. 2, para. 1). The guidance provided in the specification is limited intra muscular injection of an AAV vector encoding the murine FIX transgene (1 X 10^{11} vector genomes/mouse) with or without immuno modulation therapy to a hemophilia knockout mouse. The specification fails to correlates the data in mouse model whose genome comprises disruption in FIX gene such that no protein is produced to the breadth of the claims embracing delivering to a rAAV containing gene encoding Factor IX to any mammal having any genetic defect that can produces FIX antibodies. Prior and post filing art teaches that gene therapy approaches that are effective in inbred mice often fail in humans and other larger mammals. Ponder et al (Current Opinion Hematol, 2006, 13, 301-307, art of record) describe the to difficulties in scaling up to larger animals, or to the biology of animals with a longer life span (see page 303, col. 1, last para bridging to col. 2). The specification also does not provide any guidance as to how studies in rodent model with gene knock out could be extrapolated to other mammal having any genetic defect that can produce antibody to FIX as recited in the base claim. Therefore, methods of prevention of the formation of inhibitory antibodies to Factor IX in a mouse model using AAV cannot be directly extrapolated to prevention of the formation of inhibitory antibodies to Factor IX in any other mammal having any genetic defect that can produce antibody to FIX. The guidance provided by the specification amounts to an invitation for the skilled Artisan to try and follow the disclosed instructions to make and use the claimed method. At the time of the instant invention, the skilled artisan not have been able to extrapolate from inhibiting the formation of inhibitory antibodies in mice to preventing the formation of inhibitory antibodies in any mammal undergoing gene therapy without an undue amount of experimentation.

In conclusion, in view of breadth of the claims and absence of adequate showing by Applicant, in the way of specific guidance and direction, and/or working examples demonstrating the same, such invention as claimed by Applicant is not enabled commensurate with full scope for the claimed inventions. The specification and prior art do not teach a method of preventing the formation of antibodies by administering cyclophosphamide prior or simultaneously with AAV comprising gene encoding Factor IX to a mammal having any genetic defect that can produce antibody to FIX. An artisan of skill would have required undue experimentation to practice the method as claimed because the art of gene delivery intended for

gene therapy, with any AAV comprising gene encoding FIX was unpredictable at the time of filing of this application as supported by the observations in the art record.

Response to arguments

Applicants arguments filed December 2, 2009 have been fully considered and found persuasive in part. Therefore, rejection of claims 1-2, 24, 28, 43 and 44 have been modified to indicate that specification, while being enabling for a method of preventing the formation of inhibitory antibodies to Factor IX delivered to a mouse having specific genetic disorder having symptoms of hemophilia B by way of an adeno-associated viral vector, but fails to provide an enablement for the full scope of the claimed invention as discussed above (see enablement rejection). As an initial matter, applicants' summary of prosecution history of the instant application is noted. Applicants' arguments will be discussed to the extent it pertains to the pending rejection.

Applicants' argument with respect to gene therapy by delivering AAV comprising nucleic acid encoding Factor IX in the treatment of hemophilia is enabling is persuasive (see argument page 12 and 13) and therefore rejection pertaining to this aspect of the enablement rejection is withdrawn. Applicants' arguments with respect to the withdrawn rejections are thereby rendered moot.

Applicants ague that prior art summarized by the reference of US Patent 6,093,392 to Dr. High clearly indicate that as of the filing date, delivery of Factor IX via an AAV vector was enabled and effective to produce Factor IX in mammals lacking the same (see page 12, para. 2).

In response, Examiner would agree that High et al show that intramuscular delivery of Factor IX via an AAV vector was enabled and effective to produce Factor IX in mammals. However, applicants should note that claims are directed to a method of preventing the formation of inhibitory antibodies to Factor IX delivered to a mammal by way of an adeno-associated viral vector, wherein said mammal has a genetic defect which can result in generation of inhibitory antibodies to Factor IX. As recited instant claim embrace delivering AAV comprising nucleic acid encoding FIX to a mammal having any defect that "can" produce antibody to FIX. It should be noted that independent claim does not require genetic defect to mammal causing hemophilia or resulting in no detectable expression of endogenous F-IX. In fact, breadth of base claim read

on any genetic defect to a mammal that could result in generation of inhibitory antibody to FIX. In this regard, prior art of High et al (US patent no 6,093,392) shows intramuscular dose of AAV-cF.IX ($7x10^{13}$) to Dog 45 did not produce detectable antibodies specific for cF.IX, by Western blotting, ELISA assays and coagulation inhibitor screens at weeks 7, 13, 17, and 20. It is also reported that the dog treated with higher dose had no detectable antibodies specific for cF.IX as measured by ELISA through week 9 (See High et al US Patent 6,093,392, col. 21, lines 8-65). It is further noted that High et al used a canine model of hemophilia, wherein dogs have a point mutation in the catalytic domain of the F.IX gene, that render the protein unstable thereby causing severe hemophilia B (See Evans et al., 1989, Proc. Natl. Acad. Sci. USA 86:10095-10099, IDS). Thus, it is apparent from the disclosure that genetic defect caused by point mutation in cFIX gene in the dog disclosed by High did not produce antibodies to Factor IX following intramuscular dose of AAV-cF.IX ($7x10^{13}$). An artisan would have to perform undue experimentation to first identify the genetic defect that can produce antibody to Factor IX and then adminster rAAV comprising Factor IX to make and use the invention. It is emphasized that Examiner has cited several post filing art to support the argument that underlying mutation, the vector, the route of administration, the presence or absence of a tissue-specific promoter, and the dose are some of the factor responsible for the inhibitor formation in the setting of FIX gene transfer (supra).

Furthermore, a reading of the specification indicates, the genetic defect is the lack of Factor IX expression, so that upon administration of supplementary Factor IX, the patient develops antibodies to the supplementary Factor IX. The genetic defect does not directly cause antibody product. Thus, the claim is not enabled because the specification does not identify any defect "which can result in generation of inhibitory antibodies to Factor IX." The genetic defect that produces Factor IX deficiency is the one that causes the production of Factor IX antibodies. The scope of enablement rejection above reflects this.

Applicants argue that different AAV serotypes give rise to differing levels of expression of the transgene (Ponder et al). Applicants' assert that although expression varied, production of Factor IX was measurable. Thus, other serotypes of AAV are clearly able to transduce target cells and give rise to Factor IX production which may give rise to an unwanted inhibitory

antibody response. It is a purpose of the present method to inhibit the formation of such antibodies.

Such is not found persuasive because genetic defect caused by point mutation in cFIX gene in the dog disclosed by High did not produce antibodies to Factor IX. It is true hat variable expression may produce measurable FIX, but there is no evidence on record that AAV comprising nucleic acid encoding FIX would produce inhibitory antibody in mammal having any genetic defect. The guidance provided in the specification is limited intra muscular injection of an AAV vector encoding the murine FIX transgene ($1 X 10^{11}$ vector genomes/mouse) with or without immuno modulation therapy to a hemophilia knockout mouse. The specification fails to correlates the data in mouse model whose genome comprises disruption in FIX gene such that no protein is produced to the breadth of the claims embracing delivering to any site, any serotype, and dose of AAV containing gene encoding Factor IX to a mammal having any genetic defect that can produces FIX antibodies. The art teaches that potential factors that may increase the risk of inhibitor formation with increased vector dose per site include increased likelihood of transduction of professional antigen-presenting cells (APCs), increased local cF.IX antigen concentrations resulting in increased likelihood of effective peptide presentation, increased number of viral particles that may activate APCs (Herzog et al, Human Gene therapy, 13:1281–1291 2002, page 1289, col. 2, para. 3).

Applicants' argue that in each of the studies introduction of transgene encoding Factor IX using AAV vectors of different serotypes and administered via different routes resulted transgene expression in the treated mammal, and expression would give rise to an undesirable immune response which can be inhibited by cyclophosphamide (see page 14, last para.).

Such is not found persuasive for the reasons discussed above (See High et al). High et al (US patent no 6,093,392) shows intramuscular dose of AAV-cF.IX ($7x10^{13}$) to Dog 45 and B46 showed sustained expression of FIX but did not produce detectable antibodies specific for cF.IX. Furthermore, there is no requirement that the mammal of base claim is having genetic defect consistent with hemophilia of has no endogenous Factor IX. As stated before expression of FIX by delivery of AAV does not mean that method would prevent the inhibitory antibody to Factor IX as formation of antibodies is dependent on the underlying mutation or defect as discussed above.

Conclusion

No Claims allowed.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Smith et al (Gene Therapy (1996), 3(6), 496-502) and Dwarki et al (WO9906562).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ANOOP SINGH whose telephone number is (571)272-3306. The examiner can normally be reached on 9:00AM-5:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on (571) 272- 4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Deborah Crouch/
Primary Examiner, Art Unit 1632

Anoop Singh
AU 1632